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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/733,893	12/11/2003	Michael S. German	02307O-138122US	2608

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EXAMINER	
POPA, ILEANA	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 06/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/733,893	GERMAN ET AL.	
	Examiner	Art Unit	
	Ileana Popa	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12/11/2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office Action.

2. Claims 1-30 have been cancelled.

Claims 31-34 are pending and under examination.

Response to Arguments

Double Patenting

3. Claims 31, 33, and 34 remain rejected under the obviousness-type double patenting as claiming the same invention as claims 1, 3, 5, and 9 of the U.S. Patent No. 5,885,971, since Applicants did not submit a terminal disclaimer.

4. Claims 31-34 remain rejected under the obviousness-type double patenting as claiming the same invention as claim 6 of the U.S. Patent No. 6,004,944, since Applicants did not submit a terminal disclaimer.

5. Claims 31, 33, and 34 remain rejected under the obviousness-type double patenting as claiming the same invention as claims 1, 2, 4, 7, and 8 of the U.S. Patent No. 6,255,289, since Applicants did not submit a terminal disclaimer.

6. Claims 31-34 remain rejected under the obviousness-type double patenting as claiming the same invention as claim 1 of the U.S. Patent No. 6,531,455, since Applicants did not submit a terminal disclaimer.

7. Claims 31-34 remain rejected under the obviousness-type double patenting as claiming the same invention as claims 1, 3, and 5 of the U.S. Patent No. 6,566,342, since Applicants did not submit a terminal disclaimer.

Claim Rejections - 35 USC § 103

8. Claims 31-33 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Hickman et al. (Human Gene Therapy, 1994, 5: 1477-1483), in view of Yang et al. (Proc Natl Acad Sci USA, 1993, 90: 4601-4605).

Applicant's arguments filed on 04/25/2006 have been fully considered but they are not persuasive. Applicants traversed the instant rejection on the grounds that the cited art lacks the motivation sufficient to impel one skilled in the art to achieve the instant invention because Hickman and Yang discuss two different approaches for liver-directed gene expression, each approach targeting different cell types. Applicants argue that, when the teachings of these references are considered in their entirety, the skilled artisan would not view the approach discussed in Yang as advantageous for modification of Hickman, particularly in the context of naked DNA. Applicants continue arguing that Yang's intraductal delivery would be viewed as having disadvantages for achieving gene expression in hepatocytes as discussed by Hickamn and therefore, the

skilled artisan would not look at Yang to modify the teachings of Hickman. Moreover the skilled artisan would view Yang as teaching away from the Examiner's proposed combination because Yang points to the biliary epithelial cells as the primary target for the treatment of CF via gene transfer, and specifically teaches away from other strategies that focus exclusively on the hepatocyte as a target cell. In Applicants' opinion, Yang does not teach efficient gene expression into hepatocytes using intraductal delivery because Yang teaches that only the maximal dose of adenovirus achieved a significant gene expression in hepatocytes, and using the next highest dose, gene expression was observed in less that 1% of the hepatocytes and since adenoviral vectors are generally known to be more efficient for achieving gene expression than transfection with naked DNA the skilled artisan would view Yang as teaching away from the use of naked DNA, as claimed, for achieving efficient gene expression in hepatocytes by intraductal delivery. Additionally, Applicants disagree with the Examiner's assertion that Yang provides a motivation to modify Hickman for the same reasons discussed above. Therefore, the skilled artisan, reading Hickman and Yang and seeking to achieve sufficient gene expression in hepatocytes, would not be motivated to use intraductal delivery of naked DNA in place of Hickman's approach of direct injection into the liver. For these reasons Applicants request that the withdrawal of the rejection.

Contrary to Applicants arguments regarding the motivation to combine, the prior art clearly teaches that hepatic intraductal administration of naked DNA is an efficient way to deliver proteins to the bloodstream for the following reasons. First, Hickman et

al. teach that only the hepatocytes immediately adjacent to the injection site were transfected by using their method (p. 1480, column 1, last paragraph, column 2, last paragraph, and p. 1481, column 2, last paragraph). Therefore only a few hepatocytes need to be transfected with the naked DNA in order for the protein to appear into the bloodstream. Second, Yang et al. clearly teach that hepatocytes can be transfected via intraductal delivery of adenoviral constructs and that the dose of administered adenoviral constructs can be manipulated such that the desired cell type is preferentially transfected. Yang et al. teach that more than 80% hepatocytes can be transfected by using high doses of adenovirus (p. 4603, column 1, second paragraph) and that lowering the dose by 10-fold results in less than 1% transfected hepatocyte, still enough to result in delivery to the bloodstream, according to the teachings of Hickman et al. Therefore, one of skill in the art, reading Hickman and Yang and seeking to achieve sufficient gene expression in hepatocytes would have been motivated to use intraductal delivery of naked DNA in place of Hickman's approach of direct injection into the liver because Yang et al. clearly teach the advantage of intraductal delivery for gene therapy (p. 4603, column 2, Conclusions). One of skill in the art would have had known to vary the concentrations of naked DNA to be administered intraductally with the purpose of optimizing the amount of protein delivered to the bloodstream. Absent evidence to the contrary, it is generally not inventive to discover the optimal working conditions of a prior art method, such conditions can be identified by routine experimentation. Third, since Hickman et al., taken with Yang et al., teach the same delivery method as the one

claimed by the instant application, their method must necessarily be as efficient as the claimed method in delivering proteins to the bloodstream.

9. Claim 34 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Hickman et al. taken with Yang et al., as applied to claims 31-33 above, in further view of Heartlein et al. (Proc Natl Acad Sci, 1994, 91: 10967-10971).

Applicant's arguments filed on 04/25/2006 have been fully considered but they are not persuasive. Applicants traversed the instant rejection on the grounds that Heartlein discusses *in vivo* delivery of human growth hormone (HGH) by transplantation of genetically engineered primary fibroblasts expressing HGH. Applicants argue that Heartlein does not teach intraductal delivery of a DNA into a secretory gland and therefore does nothing to cure the deficiencies of Hickman and Yang. Accordingly, a *prima facie* case has not been established with respect to claim 34 and, therefore, the withdrawal the withdrawal of the rejection is requested.

Contrary to Applicants' arguments, Hickman et al., taken with Yang et al., clearly teach the claimed invention (see above). Heartlein et al. reference was cited because it does teach that gene therapy can be used to treat HGH deficiencies. As stated in the prior Office Action, although Hickman et al., taken with Yang et al. do not teach HGH, one of skill in the art would have been motivated to use the method of Hickman et al. and Yang et al. to deliver HGH to the bloodstream of a subject because Heartlein et al. do teach that growth hormone deficiencies can be treated by steady-state delivery of

HGH via gene therapy. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Conclusion

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ileana Popa

JANET L. EPPS-FORD, PH.D.
PRIMARY EXAMINER